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Adolescent cannabis use

What is the evidence for functional brain alteration?

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REVIEW ARTICLE

Adolescent Cannabis Use: What is the Evidence for Functional Brain Alteration?

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Abstract: Background: Cannabis use typically commences during adolescence, a period during which the brain undergoes profound remodeling in areas that are high in cannabinoid receptors and that mediate cognitive control and emotion regulation. It is therefore important to determine the impact of adolescent cannabis use on brain function.

Objective: We investigate the impact of adolescent cannabis use on brain function by reviewing the functional magnetic resonance imaging studies in adolescent samples.

Method: We systematically reviewed the literature and identified 13 functional neuroimaging studies in adolescent cannabis users (aged 13 to 18 years) performing working memory, inhibition and reward processing tasks.

Results: The majority of the studies found altered brain function, but intact Behav task performance in adolescent cannabis users versus controls. The most consistently reported differences were in the frontal-parietal network, which mediates cognitive control. Heavier use was associated with abnormal brain function in most samples. A minority of studies controlled for the influence of confounders that can also undermine brain function, such as tobacco and alcohol use, psychopathology symptoms and family history of psychiatric disorders and substance use.

Conclusion: Emerging evidence shows abnormal frontal-parietal network activity in adolescent cannabis users, particularly in heavier users. Brain functional alterations may reflect a compensatory neural mechanism that enables normal Behav performance. It remains unclear if cannabis exposure drives these alterations, as substance use and mental health confounders have not been systematically examined.

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1. INTRODUCTION

Adolescence is a critical period for experimenting with psychoactive substances including cannabis. Cannabis is the most highly consumed illicit drug worldwide, with typical ages of onset ranging between 16 and 19 years [1]. Annual prevalence rates of adolescent cannabis use (*i.e.*, 12, 14 and 16 years of age) fluctuated over the past 15 years, with decreases from year 2002 to 2006, and increases from year 2007 onwards [2]. Adolescent cannabis use may interfere with brain development [3-5]. Exposure to exogenous cannabinoids alters the endocannabinoid system [6], which is critical for shaping key neurodevelopmental processes (*e.g.*, regulates synaptic connectivity [7, 8] and plasticity [9], in the adolescent brain and contributes to determine connectivity patterns [10]). Further, the main psychoactive compound of cannabis, delta-9-tetrahydrocannabinol (THC [11]), can have neurotoxic effects in rodents and primates [12-14] and psychotogenic properties in humans [15, 16]. THC levels in the commonly smoked cannabis are high and have been increasing over time [17, 18], suggesting that the potential adverse effects of cannabis on the developing brain may also be increasing.

Prefrontal, parietal and temporal brain regions [19-22] may be particularly vulnerable to the adverse effects of cannabis use during adolescence, as they have a high density of cannabinoid receptors [23, 24], undergo marked neuroanatomical changes during neurodevelopment, and regulate emotion, reward [25, 26] and cognitive processes - the refinement of which occurs during adolescence [27]. Mental health problems and cognitive impairment are commonly observed in adolescent cannabis users, including psychotic, depressive and conduct disorders [28, 29], and poorer learning, memory, attention and impulsivity [30-32]; these outcomes may be linked to alteration of the above-mentioned brain regions. Studying the neural substrates of adolescent cannabis use is important given that neural deficits may mediate cognitive and emotion impairments in adolescent users, which can persist throughout adulthood [33-37] and have a broader functional impact on future outcomes (*e.g.*, school and work performance, low socioeconomic status, poorer educational achievement [38-40]). Furthermore, investigating the neurobiology of adolescent cannabis use is a timely issue in light of the recent global trends towards decriminalisation of cannabis products [41].

Several reviews have summarized evidence on the influence of cannabis on brain function [42-46]. The two most recent reviews of functional Magnetic Resonance Imaging (fMRI) studies of adolescent cannabis users highlight abnormalities in the function of prefrontal and parietal cortices [45, 46]. These reviews, based on only 5 [45] or 11 studies [46], could not draw strong conclusions on the nature of brain functional abnormalities in adolescent cannabis

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users (*i.e.*, direction of alteration, which cognitive domains are most consistently linked to brain alterations, whether cannabis versus other variables drive the alterations). The studies reviewed at that time were largely focused on the same cognitive domain - spatial working memory - leaving the neural substrates of multiple other domains relatively unexplored (*e.g.*, inhibition, reward processing, decision making, verbal learning and memory). Further, no review to date has exclusively focused on the fMRI evidence in adolescent cannabis users, preventing a comprehensive examination of the literature to date. Careful consideration must be given to the characterisation and measurement of cannabis and other substance use, the mental health of the samples examined to date, approaches undertaken to disentangle the impact of cannabis versus these and other potential confounders entrenched with cannabis use, as well as in depth examination of the tasks employed, MRI analysis approach and ultimate functional brain findings and their interpretation. Thus, we are currently unable to delineate in detail, the gaps in knowledge in the evidence to date, and to inform future directions.

This review integrates the most recent evidence on fMRI studies of adolescent cannabis users to characterise more accurately the neural substrates of adolescent cannabis use. First, we overview sample characteristics of the included studies with a focus on demographics (age, gender), cannabis use, mental health and cognitive performance, and the confounders controlled for in analyses. Second, we overview results pertaining to group comparisons (cannabis users versus nonusers) in brain activity across the cognitive domains of interest. Third, we summarise the emerging associations between brain activity and chronicity of cannabis use, and other relevant variables (psychopathology symptoms, use of substances other than cannabis, task performance). Finally, we discuss the themes emerging in the fMRI literature in adolescent cannabis users, identify limitations and suggest future directions to advance research in this field.

2. MATERIALS AND METHODS

We conducted a search in PubMed using the terms: "cannabis"[All Fields] OR "marijuana"[All Fields] AND (("humans"[MeSH Terms] AND "adolescent"[MeSH Terms])) AND (fMRI[All Fields]). We applied the search limits: i) samples aged ≥ 13 and ≤ 18 years; ii) human species; iii) studies published between 1st January 2000 and 7th October 2015. This search led to the identification of 116 studies, which were screened against a number of criteria. We included studies that implemented fMRI methodology and investigated samples of regular cannabis users as defined by each study protocol, with wide-ranging periods of abstinence prior to scanning. We excluded studies if they: i) investigated samples with any comorbid diagnosable psychopathologies or any neurological disorders; ii) were non-empirical (including review articles and case studies) or investigated non-human species. A final count of 13 studies were identified and included in this review [47-59].

3. RESULTS AND DISCUSSIONS

3.1. Participant Recruitment and Assessment

3.1.1. Recruitment Sites

The identified studies (but [59]) reported recruiting participants from local high schools [50, 52-55, 57, 58], colleges [56, 57], local community [51], the Internet [49, 54] or local substance abuse support councils and health and resource centres for adolescents who were involved with the legal system for drug possession [49, 54], and two studies recruited from substance treatment services [47, 48].

3.1.2. Substance Use Assessment

All investigations performed substance use and/or dependence assessment based on the DSM-IV criteria [60] using a wide variety

of instruments. Cannabis Use Disorders (CUDs) were assessed with the *World Health Organization Composite International Diagnostic Interview Short-Form (WHO CIDI-SF)*; [61]) in one study [47], the *K-SADS-PL* [62] in other study [48]; and the *Customary Drinking and Drug Use Record (CDDR)*; [63]) in two studies [52, 58].

Substance use was assessed with the *CDDR* in 6 studies [52, 53, 55-58]. Two studies employed self-report drug questionnaires [49, 54]. The *Time-line follow back calendar* [64] and the *ESPAD drug use questionnaire* [65] was used in one study [47], the *Lifetime History of Alcohol Use Interview* [66] in a separate study [48], and the *K-SADS-PL* [62] in two of them [48, 51]. Alcohol abuse and/or dependence were not assessed in six studies [47, 49, 50, 54, 56, 59]. In sum, examination of comorbid substance use was performed using a heterogeneity of measures.

3.1.3. Psychiatric Assessment

All but one study [50] reported using standardised instruments to assess psychiatric wellbeing. Most studies performed psychiatric screening using the *Diagnostic Interview Schedule for Children Predictive Scales (DPS)*; [67, 68]) [52, 53, 55-57], *Diagnostic Interview Schedule for Children-IV (DISC-IV)*; [48]) [49, 54, 58], *Structured Clinical Interview for DSM-IV (SCID)*; [[60]]) [50, 51] and the *Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Episode (K-SADS-PL)*; [62]) for participants aged <18 years [48, 51].

The reviewed studies used different criteria to exclude participants with comorbid psychopathologies: (i) any DSM-IV axis 1 disorders (*i.e.*, in all participants [55-57] and in controls only [48, 51]); (ii) psychiatric disorders other than Cannabis Use Disorders (CUDs) and Alcohol Use Disorders (AUDs) [50, 52, 53] or current AUDs only [56]; or psychiatric disorders other than (iii) conduct disorder [49, 54, 58]; or (iv) attention deficit-hyperactivity disorder [53, 55].

3.2. Sample Characteristics

3.2.1. Demographics

Demographics of the samples from the reviewed studies are provided in Table 1. The size of the investigated samples was relatively small; in most this ranged between 13 and 17 cannabis user participants ($n=7$ studies), with a minimum of 7 and maximum 28 participants in the remaining studies. The majority of the samples had an average age of 18 years ($n=7$ studies [50-53, 55-57]), followed by 17 years ($n=4$ studies [49, 54, 58, 59]) and 16 years ($n=2$ studies [47, 48]). All samples were composed either exclusively ($n=3$ studies [48, 49, 54]) or mostly of male participants ($n=11$ studies).

3.2.2. Cannabis Use Levels

All studies cross-sectionally examined cannabis user groups relative to healthy non-cannabis using controls. In most studies cannabis use was current in the user sample, with abstinence ranging from hours to days prior to scanning (*e.g.* [47, 51], or at least 2 days of abstinence [58], or a mean of 5.1 weeks prior to scanning [49, 54]). Other studies examined users following more prolonged periods of abstinence (*e.g.* more than two months [48], at least 22 days [52], at least 28 days [55-57] or with a mean of 10 months of abstinence [59]). Schweinsburg and colleagues compared recent (2-7 days) and abstinent (27-60 days) cannabis users [53] and Jacobus and colleagues (2012) compared cannabis users when they were abstinent from 1 to 17 days, and again after 28 days of abstinence [50].

All samples of cannabis users smoked cannabis for a range of 2 to 4 years and started using cannabis regularly at 13 to 16 years of age. Cannabis use was quantified in lifetime number of smoking episodes ($n=8$ studies) and number of smoked joints ($n=5$ studies, see Table 1). Lifetime exposure to cannabis was measured by the cumulative number of (i) joints consumed, ranging from $\sim 2,000$ to

Table 1. Sample demographic and cannabis use characteristics.

Author, year	Ref#	N(Female)		Age, M(s.d.)			Group matching	Level of Exposure			
		CB	HC	CB	HC	Range		Age onset	Duration, yrs	Lifetime episodes	Mean abstinence days [range]
Behan, 2014	[47]	17(1)	18(1)	16 (0.2)	16 (0.4)	14-19	Age	13	3	6,708 joints	At least the night before
De Bellis, 2013	[48]	15(0) 12*	18 (0) & 23(0)**	16 (1)	16 (1)	14-17	Age & family history of SUD	14	1	1,976 joints	134 days [60-220 days]
Jager, 2013	[49]	21(0)	24(0)	17 (1)	17 (1)	13-19	Age & hand	13	4	4,006 joints	5.1 weeks [1-16 weeks]
Jacobus, 2012	[50]	23(6)	23(4)	18 (1)	18 (1)	15-18	Age, sex, SES & family history of SUD.	—	—	398 days	5.1 days at baseline [1-17 days] Follow-up after 28 days
Lopez-Larson, 2012	[51]	24(2)	24(7)	18 (1)	18 (2)	16-19	Age, sex & hand.	16	2	1,500 joints	20 CB last use < 24h ; 3 <48h; 1 >48h
Schweinsburg, 2011	[52]	8(4) 28 (5)†	22(6)	18 (1)	18 (1)	16-18	Age, IQ, depressive and anxiety symptoms	15	3	427 days	118 days. At least 22 days
Schweinsburg, 2010	[53]	Cur: 13(4)	18(7)	17 (1)	17 (1)	15-18	Age, sex, ethnicity, SES, depressive and anxiety symptoms	16	2	342 days	3 days [2-7 days]
		Abst: 13(4)		18 (1)				15	3	515 days	38 days [27-60 days]
Jager, 2010	[54]	21(0)	24(0)	17 (1)	17 (1)	13-19	Age & hand.	13	4	4,006 joints	5.1 weeks [1-16 weeks]
Schweinsburg, 2008	[55]	15(4)	17(5)	18 (1)	18 (1)	16-18	Age, sex, ethnicity & IQ	15	3	481 days	60 days. At least 28 days
Tapert, 2007	[56]	16(4)	17(5)	18 (1)	18 (1)	16-18	Age, sex, IQ, depressive and anxiety symptoms	15	3	476 days	58.4 days. At least 28 days
Padula, 2007	[57]	17(3)	17(5)	18 (1)	18 (1)	16-18		—	—	477 days	At least 28 days
Schweinsburg, 2005	[58]	15(5) †	19(8)	17 (1)	17 (1)	15-17	Age & sex	—	—	>100 days	7.64 days. At least 2 days
Jacobsen, 2004	[59]	7(4) ††	7(5)	17 (1)	17 (1)	16-18	Age, sex & edu.	14	3	283 days	10 months [1.5-24 months]

CB: cannabis users; HC: healthy controls; Cur: current cannabis users; Abst: abstinent cannabis users; Age onset: mean age of onset of use [47, 49, 54, 59]; of regular use [48, 51, 56]; of weekly use [52, 53, 55, 58]; age of onset of CUD [53, 57]; Lifetime episodes: mean number of lifetime joints or episodes; Abstinence days: mean, range or minimum days of abstinence before the scan; SUD: substance use disorder; SES: socioeconomic status; IQ: intelligence quotient; Depressive symptoms measured by the BDI Anxiety symptoms measured by the STAI; *CUD individuals who relapsed within 1 year; **controls with psychopathology matched those with a CUD; † Cannabis + alcohol use disorder [52, 58]; ††Cannabis and also tobacco smokers [59]

~7,000 [47-49, 51, 54]; or (ii) smoking episodes, which ranged from ~280 to 4,000 [50, 52, 53, 55-59]. Most samples smoked cannabis approximately on a mean of 400 occasions (range from 427 to 481 occasions, as shown in Table 1 [52, 55-57]).

Four studies examined cannabis users who endorsed a current or history of CUD [47, 48, 52, 58]. Of these, two samples were recruited from treatment services and endorsed a diagnosis of current [47], or fully remitted CUD (7 and 6 participants with dependence and abuse, respectively [48]). The other two samples were recruited from the general community, and endorsed a diagnosis of current CUD alone (in 50% of participants [52] and

with comorbid AUDs [58]. Information on diagnostic assessment and screening of CUD was not provided in the remaining 9 studies.

3.2.3. Mental Health

Psychiatric comorbidity in the samples included: (i) conduct disorders in 5 studies [48, 49, 53, 54, 56, 58]; (ii) AUDs in 6 studies, in two of which AUDs were endorsed in all participants [53, 58]; and in four of which they were endorsed in a portion of cannabis users only (*i.e.*, ≤4 participants with either heavy alcohol use or abuse, current or past alcohol dependence) [48, 51, 55, 57]; and (iii) comorbid depression, anxiety and other psychiatric disorders in one sample [48].

Fig. (1). Heat map representing the number of studies that examined confounding variables and their influence on brain function.

3.3. Assessment of Confounding Variables

The majority of studies measured confounding variables that may affect brain function and brain development, including socio-demographic characteristics, psychopathology symptoms, and use of substances other than cannabis (see Fig. 1). A portion of these variables was matched between cannabis users and controls, and only a minority of studies controlled for the confounding influence of these variables on the study results.

Colored cells indicate the number of studies for each variable in each category. Red indicates low number of studies and green high number of studies, as indicated by the color bar on the right side. IQ: intelligence quotient; GAF: Global Assessment of Functioning [69]. **Reported** = Number of studies that report data on the variables listed in the y axis; **Group-matched** = number of studies that find no statistical differences between cannabis users and controls or excluded from both groups, participants with comorbidities or family history of psychiatric disorders; **Group differences** = number of studies that found statistical differences between groups in the variables listed in the y axis; **Controlled for** = number of studies that controlled for confounding variables via using them as covariates in the analyses [49, 54], repeating the analyses with these variables as covariates [47, 48, 50, 52, 54-56], or repeating the analyses excluding participants with alcohol use disorder [55], conduct disorder [53] or smoked cannabis on the day of MRI assessment [55].

3.3.1. Confounding Variables Reported in the Studies

With one exception [51], all studies reported data on age, gender and IQ. Ten studies reported data on anxiety and/or depression symptoms using scales (all but three studies [49, 54, 58]) or assessing the presence of anxiety or depressive disorders in the sample [48]. Ten studies provided information regarding the presence of conduct disorder in cannabis users and healthy controls, five of which excluded participants with this comorbidity [50, 52, 55-57]. All studies reported data on alcohol use, and all but one

[51] reported tobacco use and/or nicotine dependence. Other psychoactive substance use information was reported in all studies but two [51, 59]. Approximately half of the studies reported data on family history of substance use [48, 50, 52, 55-58, 70], family history of psychiatric disorders [55-58, 70], household income [50, 52, 55-58, 70] and participants' level of education measured as years [47, 59] or grades [50, 56, 58]. Only one study reported on parental level of education [59] and participants' level of global functioning [51].

3.3.2. Confounding Variables: Group Matching or Group Differences

Potential confounding variables including gender, education level and family history of substance use/psychiatric disorders (participants with family history of psychiatric disorders were excluded from study participation), were group-matched in all of the studies that considered these confounders. Age was only significantly different in one study between cannabis users who endorsed CUDs and controls with psychopathology, but not between CUD participants and healthy controls [48]. IQ, anxiety and depression symptoms, and household income were group-matched in six studies. Within several samples, cannabis users endorsed more conduct disorder comorbidity (4 of 10 studies assessing this variable) and higher levels of alcohol (10 of 12 studies), tobacco (7 of 12 studies) and other substance use (6 of 11 studies) than controls. Parents' educational level and participants' global functioning were lower in cannabis users than controls in the 2 studies that respectively examined these variables [51, 59].

3.3.3. Confounding Variables: Controlled for in Analysis

Some studies controlled for the influence of confounding variables in their analyses, using confounders as covariates [49, 54], repeating analyses with and without using confounders as covariates [47, 48, 50, 52, 54-56], or rerunning analyses with and without participants with AUD [55], conduct disorder [53] or cannabis consumption on the day of MRI assessment [55] (see Fig.

1). Single studies controlled for the influence of key demographic variables such as age [49, 54], gender [52] and IQ [54]. Level of use of substances other than cannabis, such as alcohol, tobacco and additional psychoactive substances, were controlled for in 50% [48, 50, 54-56], 86% [47, 48, 50, 54-56] and 50% [50, 52, 56] of studies that found significant differences between groups, respectively. A minority of studies controlled for the influence of sub-diagnostic psychiatric symptoms, with only one study controlling for anxiety symptoms [55], two studies controlling for depressive symptoms [55, 56] and one study repeated the analyses excluding participants with conduct disorder [70]. Family history of psychiatric disorders and substance use was controlled for in one study [56]. Results from group comparisons remained unaltered after controlling for the influence of confounders.

3.4. Behav Performance

Table 2 summarises the employed experimental tasks, relevant cognitive domains, group differences in Behav performance, and brain functional outcomes. Working memory was the most commonly examined cognitive domain (n=6 studies; [53-55, 57-59]). Two studies each examined associative learning [52, 54]; inhibitory control [47, 56], and reward processing [48, 49]. Single studies examined motor functioning (*i.e.*, reaction time [51]) and brain connectivity during rest [71]. Table 2 shows two investigations reported less accurate working memory and poorer inhibition in cannabis users, relative to controls [47, 59]. No other statistically significant group differences in task performance were found. Two studies reported a trend for reduced performance during working memory [53] and reward processing, with slower reaction times during reward relative to neutral trials [49] in cannabis users versus healthy controls. Working memory deficits were not observed in samples after prolonged [54, 55, 57] or recent abstinence from cannabis [58]. Similarly, inhibition deficits were not observed in 28-day abstinent cannabis users [56]. These findings suggest that the cognitive and brain function impairments observed in cannabis users can be ameliorated and recovered through prolonged abstinence.

3.4.1. fMRI Findings

Ten out of the 13 studies found group differences in brain function between adolescent cannabis users and healthy controls (see Fig. 1 [47-51, 54-57, 59]). Differences in brain activity were also found when comparing current versus abstinent cannabis users [53] and adolescents with CUDs and comorbid AUDs, relative to controls [52, 58]. As shown in Fig. 2, differences in task-related brain activity between cannabis users and controls were most consistently reported in the inferior parietal cortex (n=6 studies, bright green in Fig. 2), the anterior cingulate cortex (ACC, n=5 studies), and superior frontal and superior parietal regions (n=4 studies). Abnormal function of cerebellar and sub-genual regions (n=2 studies) and medial prefrontal, posterior regions (n=1 studies) were also reported.

3.4.1. Employed Analysis Approach (ROI and Whole Brain)

All studies carried out whole-brain analysis (with one exception [59]) and seven studies focused on a specific ROI [47-49, 51, 52, 54, 59] (one of these used separate ROIs for two different tasks [54]). Amongst whole brain studies, most of those that examined spatial working memory found differences between cannabis users and controls [53, 55, 57, 58] (with one exception [54]). Further differences emerged in one (*i.e.*, lower cingulate activity [47]) of the two studies that examined inhibition [47, 59], and in single studies of motor functioning [51]; and resting state [50]. Non-significant group differences between cannabis users and controls were found using the whole brain approach, for two studies of verbal learning [52, 54] and single studies of reward processing [49].

Most studies that used a ROI approach found differences between cannabis users and controls (n=6 of 7 [47-49, 51, 52, 54, 59]; one of these used separate ROIs for two different tasks and only

one was significantly different between groups [54]). ROIs included the frontal lobule (orbitofrontal cortex [48], superior and middle frontal gyrus [51, 54], inferior [47]), the cingulate cortex in two studies [51, 54] (*i.e.*, one of which examined this region in two different tasks [54]), and the hippocampus/parahippocampus in three studies [52, 54, 59], the cerebellum [47, 51] and parietal cortex in two studies [47, 54]. Single studies examined the dorsal lateral prefrontal cortex (DLPFC) [54], caudate and putamen [49], and occipital regions [54]. The only studies that did not find a group difference in brain activity included one study of verbal learning that examined the hippocampus [52]; and a separate study of visual memory that focused on the para-hippocampus, middle occipital, DLPFC and anterior cingulate cortex regions [54]. Overall, either a whole brain or ROI approach revealed significant alterations in most samples of cannabis users.

3.4.2. Findings on Brain Activity in Cannabis Users, by Examined Cognitive Domain

Overviewing the findings by examined cognitive domain, revealed consistent abnormalities in the frontal-parietal network. For working memory, cannabis users showed lower activity in the DLPFC [55], inferior frontal gyrus and temporal cortex [58, 59]; parietal cortex [54, 55, 57]), medial prefrontal cortex [54, 55, 58]) and basal ganglia [57]. During inhibition, cannabis users versus controls, showed higher connectivity [47] and activity in parietal and prefrontal cortex and insula [56]. Higher neural activity was also observed during decision making, in current cannabis users versus controls, for the caudate and putamen (*i.e.*, anticipation of neutral trials [49]), parietal and occipital cortices (*i.e.*, prediction of uncertain outcome [48]); while lower activity was observed in current cannabis users versus controls while receiving rewards [48] and in abstinent cannabis users who relapsed versus 12-month abstinent cannabis users, in prefrontal, parietal, occipital and orbitofrontal regions [48]. This indicates mixed findings for decision making-related brain activity, with both increase and decrease in brain activity during task performance, and lower activity with abstinence, requiring replication in additional samples.

Resting state studies revealed that cannabis users showed higher task-based functional connectivity in parietal-cerebellar regions [47], higher resting-state activity in supramarginal gyrus and lower activity in cuneus, temporal, insula, and prefrontal medial frontal gyrus relative to controls [50]. These alterations during rest were not observed after 28 days abstinence [50]. The two studies that investigated brain function during associative learning tasks showed mixed findings. While no significant differences were found between cannabis users and controls [52, 54], higher prefrontal activity was observed in a subgroup of 'pure' cannabis users relative to comorbid cannabis and alcohol users, and to controls [52]; and lower occipital activity was observed in comorbid cannabis and alcohol users versus controls [52]. The mixed location and direction of alterations, and heterogeneous sample composition (*i.e.*, presence and absence of comorbid alcohol use in different studies) prevent to draw conclusions on the neural substrates of associative learning in adolescent cannabis users. Finally, during a motor task, lower cingulate and cerebellar activity was observed in cannabis users [51].

3.4.3. Associations Between Brain Activity and Substance Use, Psychopathology Symptoms and Task Performance

All studies explored the association between brain activity and cannabis use frequency, quantity and age of onset (with two exceptions [52, 57]), and all reported (positive and negative) associations, as shown in Table 3. Only 6 of 13 studies examined the relationship between brain function and alcohol, tobacco and other drug use [48, 50, 52, 53, 55, 56]. Most of these studies (n=5) found significant correlations between use of alcohol, tobacco [50, 55], and other substances [48, 52, 56] and brain function in prefrontal and parietal regions (see Table 3).

Table 2. Summary of examined cognitive domains, employed tasks and fMRI results.

Author Year	Ref#	Cognitive domain	Task	Behavioural performance	Brain activity, group comparison	
					Whole brain analysis	ROI analysis
Behan 2014	[47]	Inhibition	Go/No-go task	CB<HC in N of successful inhibitions. CB=HC for RT in Go, No-Go & omissions rate	CB<HC in anterior cingulate (adjacent white matter tracts).	ROI=2 networks: 1) parietal & cerebellum 2) IFG, parietal & cerebellum. <u>During successful inhibition</u> , CB>HC for correlation within 2 networks. <u>During rest</u> , CB>HC in correlation within network 1
De Bellis 2013	[48]	Decision-making (behavioural risk, reward risk, reward no-risk)	Decision-Reward Uncertainty	CUD either with or without relapse = either HC or HC* for RT and number of successful runs in decision-making and reward phases	<u>During decisions leading to uncertainty of reward vs. those leading to rewards</u> , CUD>HC* for activity of superior parietal lobule, lateral occipital cortex & precuneus. <u>While receiving vs. not receiving rewards</u> , CUD<HC and HC* for IOFC activity.	ROI=IOFC IOFC activity during rewards in CUD who relapsed within 1 year < abstinent CUD.
Jager 2013	[49]	Reward	MIDT	Trend for RT in CB>HC for reward vs. neutral trials	CB=HC for anticipation and feedback.	ROI= caudate & putamen <u>Anticipation of neutral trials</u> : CB>HC in left caudate, & trend for right caudate and right putamen <u>Anticipation of reward trials</u> : CB=HC <u>Feedback</u> : CB=HC
Jacobus 2012	[50]	Resting state	—	—	At baseline, CB<HC for CBF in superior and middle temporal lobe, insula, supramarginal gyrus & MFG At baseline, CB>HC in precuneus. At follow-up following 28 day abstinence, CB=HC.	-
Lopez-Larson 2012	[51]	Motor	Finger tapping (bilateral)	—	CB<HC for cingulate gyrus, trend CB>HC middle occipital gyrus	ROI= SFG, MFG, cerebellum & cingulate cortex CB<HC for cingulate & anterior cerebellum activity (trend for posterior cerebellum).
Schweinsburg 2011	[52]	Verbal pair associate learning	VPA	CB, CB+AUD=HC	<u>Main effect for cannabis use</u> : No differences <u>Drinking x Cannabis interaction</u> : CB > HC, CB+AUD for SFG, IFG, & MFG activity CB, AUD < HC (and AUD<CB+AUD) for cuneus & lingual activity CB+AUD = HC	ROI=hippocampus CB=HC
Schweinsburg 2010	[53]	Spatial WM	SWM	Trend for faster RT in Curr.>Abst. & HC for vigilance. Trend for faster RT in abst than current & HC for spatial WM	<u>For spatial WM relative to vigilance</u> : Curr. CB>Abst. CB for medial cingulate, MFG, IFG & SFG, insula and precentral activity. In frontal and insular regions Curr. greater activity, Abs. reduced activity, HC no difference. Abst. > Curr. CB for activity in right precentral gyrus.	-

(Table 2) Contd....

Author Year	Ref#	Cognitive domain	Task	Behavioural performance	Brain activity, group comparison	
					Whole brain analysis	ROI analysis
Jager 2010	[54]	Verbal WM	STERN	CB=HC for RT & accuracy. Older age a/w faster RT & higher accuracy.	CB=HC for WM activity measured by novel vs. RT control task, practice vs. RT control task.	ROI= IFG, DLPFC, superior parietal cortex, ACC CB>HC while learning (NT), & CB=HC after task is familiar.
		Pictorial associative memory	PMT	CB=HC for accuracy.	CB=HC for either association between 2 pictures or retrieval vs. single picture classification.	ROI=para-hippocampal gyrus, middle occipital gyrus, DLPFC, ACC. CB=HC
Schweinsburg 2008	[55]	Spatial WM	SWM	CB=HC for accuracy and RT	<u>SWM relative to vigilance</u> , CB>HC for parietal activity; and CB<HC for DLPFC & superior cuneus activity. <u>Vigilance relative to SWM</u> , CB>HC for inferior cuneus.	-
Tapert 2007	[56]	Inhibition	Go/No-go task	CB=HC	In <u>inhibition trials</u> , CB>HC for DLPFC, MFG, inferior, posterior parietal & lingual activity. In <u>go trials</u> , CB>HC for PFC, insular, and parietal cortices activity.	-
Padula 2007	[57]	Spatial WM	See refs a,b	CB=HC for accuracy & RT	During spatial WM trials, CB>HC for basal ganglia, precuneus, postcentral gyrus & superior parietal lobule activity.	-
Schweinsburg 2005	[58]	Spatial WM	See refs a,b	CB & CB+AUD=HC	During spatial WM trials: CB+AUD<HC, but >AUD, for IFG & temporal activity. CB+AUD>HC for PFC activity. CB+AUD<AUD for MFG activity. CB+AUD > AUD & HC for ACC deactivation	-
Jacobsen 2004	[59]	Auditory WM	n-back task (auditory, 2 levels of attention and 2 of WM load)	CB<HC for accuracy across tasks CB< tobacco users & HC for accuracy in dichotic 2-back	CB=HC	ROI=hippocampus CB<HC and tobacco users.

ROI= region of interest; CB= cannabis users; HC= healthy controls; RT= reaction time; IFG= inferior frontal gyrus; CUD= cannabis use disorder; IOFC= left orbitofrontal cortex; MIDT= Monetary Incentive Delay Task [72]; CBF= cerebral blood flow; MFG= medial/middle frontal gyrus; SFG= superior frontal gyrus; VPA= Verbal Paired Associates task [73]; CB+AUD= Cannabis + alcohol use disorder; AUD=alcohol use disorder; SWM= Spatial working memory [56]; Curr= Current cannabis users; Abst= Abstinent cannabis users; STERN= Stenberg's item-recognition paradigm [74]; DLPFC= dorsolateral prefrontal cortex; ACC= anterior cingulate cortex; NT=novel task; PMT= Pictorial Memory Task [75]; PFC= prefrontal cortex

Two studies explored the association between brain activity and psychopathology symptoms and found an association between anxiety levels and medial prefrontal cortex [50] or precentral/insula activity [53]. Another study found an association between the personality trait measure of agreeableness and medial frontal gyrus, inferior occipital cortex activity [55].

Only three studies examined the association between Behav performance and brain activity [55, 57, 59]; two found significant associations [55, 57, 59]. Spatial working memory performance was correlated with five clusters in temporal, anterior cingulate cortex and thalamus regions [57]. The direction of the association between brain activity and task performance was opposite in adolescent cannabis users and controls (*i.e.*, positive and negative, respectively). Superior parietal activity was positively correlated with vigilance performance [55].

3.5. Discussion

Overall, the reviewed studies showed abnormal activity within parietal, prefrontal and other brain regions in adolescent cannabis users relative to non-cannabis using controls, but minimal differences in Behav performance. Many studies found that chronicity of cannabis use was associated with altered brain function, suggesting cannabis-specific effects on brain function during adolescence. Specificity to cannabis cannot be ascertained because substance use, mental health and other confounders that can also influence brain activity were seldom controlled for and longitudinal studies are missing.

3.5.1. Location of Alterations

The observed abnormalities in brain function were most consistently hyperactivity of posterior parietal regions, followed by the

Fig. (2). Functional brain alterations in adolescent cannabis users relative to controls. Illustrative heat-map shows the number of studies that reported group differences, ranging from blue (n=1 study) to bright green (n=6 studies). Location of brain regions, based on the reported findings, is represented using the Automatic Anatomical Labeling atlas of the Statistical Parametric Mapping software (<http://www.fil.ion.ucl.ac.uk/spm/>).

Table 3. Summary of associations between brain activity, substance use, psychopathology symptoms and task performance.

Author year	Ref#	Association between regional brain activity and			
		Cannabis use characteristics	Drugs other than cannabis (alcohol, tobacco, others)	Psychopathology symptoms	Task performance
Behan 2014	[47]	(+) Parietal-cerebellar connectivity with past week & past month joints	–	–	–
De Bellis 2013	[48]	(-) IOFC activity with CUD duration (correcting for current age) N.S. influence of age of onset & number of days since last cannabis consumption on IOFC. N.S. associations for parietal activity.	(-) IOFC specific to reward receipt with drug experimentation (N individual drug classes) controlling for current age). N.S. influence of alcohol abuse & nicotine dependence on IOFC. N.S. associations for parietal activity.	–	–
Jager 2013	[49]	(-) Caudate activity during anticipation of neutral trials, with age of onset N.S. influence of lifetime, past year use & weeks since last use	–	–	–
Jacobus 2012	[50]	(-) Insular CBF with smoking days in past month N.S. influence of lifetime use .	(+) Precuneus with past month drinking days & smoked cigarettes (+) mPFC with past month drinking days N.S. influence of alcohol lifetime & other drugs use	(+) mPFC with anxiety symptoms N.S. influence of depression symptoms	–
Lopez-Larson, 2012	[51]	(-) Cingulate gyrus and cerebellum activity with lifetime episodes . N.S. influence of age of onset & urine THC levels .	–	–	–
Schweinsburg, 2011	[52]	–	(+) Precentral gyrus with total lifetime drug use	–	–

(Table 3) Contd....

Author year	Ref#	Association between regional brain activity and			
		Cannabis use characteristics	Drugs other than cannabis (alcohol, tobacco, others)	Psychopathology symptoms	Task performance
Schweinsburg, 2010	[53]	Influence of days since last cannabis use N.S. influence of lifetime cannabis use episodes, years of weekly cannabis use, cannabis use past 3 months	N.S. influence of - alcohol (lifetime use episodes, frequency of use past 3 months, abstinence duration) - tobacco (daily cigarettes, abstinence duration) - lifetime other drug use episodes	(+) Precentral gyrus & insula with state anxiety	—
Jager, 2010	[54]	Verbal WM (+) IFG activity with past year & lifetime joints . N.S. influence of age of onset .	—	—	—
		PMT —	—	—	—
Schweinsburg, 2008	[55]	Occipital cortex activity during SWM: (-) with years of regular cannabis use (+) with age of onset . N.S. influence of lifetime occasions of use & days since last cannabis use	(-) Superior parietal lobe activity with CDDR estimated blood- alcohol concentration during drinking N.S. influence of alcohol use (frequency, quantity, duration, & recency), use of cigarettes & other drugs	(+) Right MFG & Inferior Occipital cortex activity with NEO-FFI agreeableness scores N.S. influence of depressive, anxiety, externalizing & internalizing symptoms .	(+) Superior parietal activity with vigilance performance .
Tapert, 2007	[56]	(-) SFG & MFG activity in no-go trials with regular use duration . (-) SFG activity in inhibitory trials with lifetime episodes (-) SFG & MFG, posterior parietal activity with cannabis days per month (+) SFG activity in inhibitory trials with age of regular cannabis use onset N.S. influence of days since last cannabis use	(+) SFG & MFG activity in no-go with lifetime episodes of other drugs (misuse of pain medication)	—	—
Padula, 2007	[57]	—	—	—	Controls (-) Superior temporal lobule, STG, MTG & ACC activity with task performance (composite score). (+) Temporal & parahippocampal gyri, uncus, thalamus & pulvinar activity with task performance Cannabis Users (+) Superior temporal lobule, STG, MTG & ACC activity with task performance (-) Temporal & parahippocampal gyri, uncus, thalamus & pulvinar activity, with task performance
Schweinsburg, 2005	[58]	(-) MTG activity with recent use N.S. influence of days since last cannabis use	—	—	—
Jacobsen, 2004	[59]	N.S. association between hippocampal activity & cannabis use (days of cannabis use, months since last use and age of onset)	—	—	N.S. association between hippocampal activity & task accuracy or RT .

(+) positive correlation; (-) negative correlation; N.S. non-significant correlation; IOFC= lateral orbitofrontal cortex; CBF= cerebral blood flow; mPFC= medial prefrontal cortex; THC= Delta-9-tetrahydrocannabinol; IFG= inferior frontal gyrus; SWM= spatial working memory; MFG = middle/medial frontal gyrus; NEO-FFI = NEO Five-Factor Inventory [76]; SFG= superior frontal gyrus; MTG= middle temporal gyrus; ACC= anterior cingulate cortex; RT= reaction time.

ACC (both hyperactivity and hypoactivity), superior frontoparietal regions (most hyperactivity, but one study reported both hyperactivity and hypoactivity [55]), cerebellum (both hyperactivity and hypoactivity) and medial prefrontal cortices (hyperactivity). The parietal (posterior and inferior) and prefrontal (ACC, DLPFC) cortices mediate high order cognitive processes that undergo refinement during development; these include arithmetic [77] and working memory skills, and goal-directed executive functions such as inhibition, interference suppression and task switching [78]. A recent meta-analysis demonstrated that during adolescence, the task-related activity of frontoparietal regions changes with age - including decreases in parietal activity and both increases and decreases in prefrontal activity [79]. The evidence reviewed here shows most consistently hyperactivity in the frontoparietal network in cannabis using adolescents, although mixed findings must be acknowledged (*i.e.*, parietal hypoactivity, both hypoactivity and hyperactivity of the ACC and fronto-parietal network). These findings suggest that adolescent cannabis users exert more brain effort in order to meet the task's demands.

Cannabis use may influence brain development via the endocannabinoid system, as cannabinoids bind to cannabinoid receptors in prefrontal and parietal cortices [80]. Adolescent cannabis use is also associated with altered neuroanatomy of prefrontal regions [45] - including larger prefrontal volumes in cannabis using females (linked to worse executive function) and smaller volumes in males (associated with better executive function [81]). In light of these findings of neuroanatomical alterations and of the reviewed findings on brain functional alteration, adolescent cannabis use may be linked to diffuse impairments of structure-function brain development.

An alternative explanation is that the functional alteration in parietal-prefrontal regions is not cannabis-specific, but reflects task-relevant activity since most studies employed working memory paradigms and therefore probed this network. Consistently, reviews of fMRI studies in adult cannabis users versus controls show that both groups engage similar task-relevant brain networks (with similar task performance as found here for adolescents), but a different pattern of activation (*e.g.*, hyperactivity, hypoactivity [45]). Instead, evidence from non-task based measures of brain activity (resting state) in adult cannabis users [45], and from neuroanatomical studies of adolescent users [82], point to the involvement of additional affect-relevant brain regions including the striatum and the amygdala, respectively. Interestingly however, functional brain alterations in prefrontal and cerebellar regions were observed across task-based studies [45], resting studies [83], and neuroanatomical studies of adult [84] and adolescent cannabis users [83], suggesting cannabis-specific, and not task-specific effects for the prefrontal cortex and cerebellum. Yet in adolescent cannabis users, the extent to which functional alteration of the frontal-parietal network is due to cannabis-specific effects, rather than task-related, cannot be resolved as evidence to date is biased by studies of working memory/related networks versus rest and other cognitive domains.

3.5.2. Dissociation in Alteration of Behav Performance and Brain Function

Adolescent cannabis users showed a dissociation between brain functional deficits, mostly hyperactivity, and normal Behav performance. This has been previously interpreted as a brain compensatory mechanism, whereby cannabis users engage different neural mechanisms, or the same mechanism in a different fashion (*i.e.*, stronger activation of the same network) to achieve similar performance to non-cannabis users [45, 74, 85-87], although some evidence does not support this notion [88]. Also, the employed cognitive tasks are often optimised and validated to study brain activity and connectivity in imaging studies, not Behav performance. We cannot exclude, however, that the lack of deficits in Behav performance in cannabis users may be a consequence of studies having low power to detect subtle cognitive alterations. The

size of the reviewed samples was relatively small (*i.e.*, cannabis users ranged from 7 to 28 participants; and controls from 7 to 24 participants), in contrast to the larger samples of studies that have consistently found performance deficits on measures of cognition in cannabis users (*i.e.*, user samples ranged from 10 to 131 participants, controls from 10 to 750 participants [89]).

3.5.3. Cannabis Versus Confounders-Driven Effects on Brain Function?

The impact of cannabis on the adolescent brain cannot be discerned independently from that of confounders that also influence brain activity. Most studies found associations between cannabis use measures and brain function, suggesting that exposure to cannabinoids drives alteration of brain activity in cannabis users. However, most studies also found significant correlations between brain function and confounders that are commonly entrenched with cannabis use (*e.g.*, use of substances other than cannabis, psychopathology symptoms and/or diagnoses).

Despite potential confounding effects, most studies did not control for key factors associated with brain activity in their samples, even when cannabis users showed higher levels of substance use and psychopathology symptoms than controls (see Fig. 1). Moreover, many studies did not report substance use and psychopathology confounders at all. There are common neural features (*i.e.*, altered activity of prefrontal and parietal cortices) of adolescents who use cannabis and those with diagnosed psychopathologies (*e.g.*, attention deficit hyperactivity disorder [90], conduct disorder, anxiety and early onset schizophrenia [91]). It remains to be elucidated if comorbid psychopathologies contribute to brain functional alterations in the reviewed samples, although it may be difficult to fully separate the impact of cannabis use from that of entrenched confounders that are highly comorbid with use.

Interestingly, when comparing brain function between the samples that did versus did not endorse conduct disorders, those samples with comorbid conduct disorder showed no difference in brain activity in whole brain studies, and minimal differences in ROI analyses (*i.e.*, no difference in parahippocampal activity [54], trend level differences in striatal activity [49], both presence and lack of differences in parietal and prefrontal regions [54]). Conversely, there were whole brain differences in those five studies that screened for conduct disorders [50, 52, 55-57], suggesting that cannabis use alone, rather than when associated with comorbid conduct disorders, may be associated with functional brain alterations.

Similarly to psychopathology confounders, exposure to substances other than cannabis, the experimentation of which often starts during adolescence [92], was poorly examined and may have contributed to the brain alterations in adolescent cannabis users. Other factors have also been poorly examined, such as family stressors and lifestyle (*e.g.*, physical activity), which are linked to problem cannabis use in adolescence [93], and gender differences in functional brain alterations in cannabis users. Given that the sudden peak in sex hormones during adolescence affects the brain endocannabinoid system [8] and neurodevelopment in a gender dependent fashion [94], further exploration of gender effects is warranted.

There was a general lack of information regarding whether participants endorsed a diagnosis of severe CUD. The few studies that measured CUD in their samples with validated instruments, employed distinct instruments and underreported the outcome of such assessment. Adolescents with CUDs (similarly to other substance use disorders) represent the portion of users that encounters the highest burden on treatment services and is most likely to experience comorbid psychopathologies (*e.g.*, conduct disorders, depression and ADHD [95]), and less likely to complete diagnostic remissions [96]. Currently, we are therefore unable to determine from the reviewed studies if addiction to cannabis has a distinct neural substrate from recreational non-problem cannabis use, and warrants the comparison of cannabis users with or without comor-

bid conditions. This notion has been demonstrated for other substances including cocaine and alcohol, where different neural circuits are engaged in the transition from recreational to compulsive substance use [97, 98].

Additional limitations include the variability in the length of abstinence before testing, which affect brain function and prevents direct comparison of the study findings; and the difficulty in assessing the amount of THC (*i.e.*, it is difficult to measure and establish what a 'joint' means pharmacologically) and other substances that might affect cognitive performance and brain activity.

Overall, there is mounting evidence suggesting altered brain function in adolescent cannabis users, but limitations in disentangling the impact of cannabis versus confounders of brain function prevents delineating whether cannabis use - rather than variables entrenched with use - drives functional brain alterations. Worryingly, this gap in knowledge contrasts with the psychosocial harms linked to adolescent cannabis use, including lower socio-economic status, completed years in school [99], alcohol and tobacco dependence [99], and psychiatric disorders in adulthood [93, 100]. We propose that the consensus development of standardised guidelines for assessing cannabis and other substance use is required to address whether it is cannabis specifically or other variables that drive adverse brain outcomes [84].

3.5.4. The Chicken or the Egg?

The reviewed studies were cross-sectional, which prevents establishing a causal link between adolescent cannabis use and altered brain function. Abnormal brain function may predate and precipitate the onset of cannabis use and the development of psychiatric problems [15, 101]. Conversely, the presence of psychopathology diagnoses/elevated symptoms, childhood adverse experiences, which were seldom measured but can affect brain function [102], may precede the onset of cannabis (and other substances) use and drive the emerging alterations in brain function in cannabis users [46]. The role of additional factors that may affect brain function has yet to be ascertained, such as the bioBehav phenotypes related to novelty seeking or risk-taking that may confer a higher risk to experiment with cannabis [103] and have defined neural substrates (*e.g.*, limbic and paralimbic regions of the socio-affective network and the frontal-parietal and connected anterior cingulate regions of the cognitive control network [104]), as well as the genetic heritability of brain function [105]. We suggest the need for more investigations like the Dutch NEXT study in MDMA [106] and the ABCD study in the USA (<http://www.addictionresearch.nih.gov/abcd-study>) for cannabis. These initiatives would enable (i) tracking adolescents that have not yet used cannabis but have the intention to use it in the next year; (ii) comparing neurodevelopment between those who commence versus do not commence using cannabis; (iii) examining if continued use versus cessation further exacerbates these alterations, (iv) determining if the adolescent brain re-organises itself after prolonged abstinence relative to controls who have never initiated using cannabis. There is also a great need for data-sharing initiatives that examine large samples and have statistical power to examine cannabis-related research questions, such as the *ENIGMA Addiction Working Group* <http://enigma.ini.usc.edu/ongoing/enigma-addiction-working-group/>.

CONCLUSION

Adolescent cannabis use is associated with abnormal functioning (mostly hyperactivity) of parietal and frontal brain networks involved in high order cognitive functions, despite apparent normal Behav performance during fMRI optimised tasks. It remains unclear whether the observed associations between cannabis use and brain function are driven by chronic cannabis exposure, comorbid substance use and psychiatric problems, or pre-existing risk factors. To elucidate if adolescent cannabis use, rather than confounders, adversely affects brain function, further

prospective research should systematically and concurrently examine their respective influence on the adolescent brain.

LIST OF ABBREVIATIONS

ACC	=	anterior cingulate cortex
AAL	=	automated anatomical labelling atlas
AUD	=	Alcohol Use Disorders
CUD	=	Cannabis Use Disorders
DLPFC	=	dorsal lateral prefrontal cortex
IFG	=	inferior frontal gyrus
IQ	=	intelligence quotient
MFG	=	medial frontal gyrus
ROI	=	region of interest
THC	=	tetrahydrocannabinol

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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